UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,997	06/20/2003	Kenneth P. Murphy	A-71608/TAL/DHR (465174-4	5773

32940 7590 03/21/2006

DORSEY & WHITNEY LLP
555 CALIFORNIA STREET, SUITE 1000
SUITE 1000
SAN FRANCISCO, CA 94104

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,997	MURPHY ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006 and 27 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64,67,68,70,71 and 73-92* is/are pending in the application.

4a) Of the above claim(s) *1-63 and 79-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,67,68,70,71,73-78 and 88-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment/remarks, filed 01/20/2006 and 01/27/2006, are acknowledged.

Claims 65, 66, 69, and 72 have been cancelled.
Claims 64, 67, 68, 70, 71, and 73 – 75 have been amended.
Claims 88 – 92 have been added.

Claims 1 – 64, 67, 68, 70, 71, and 73 – 92 are pending.

2. Applicant's election without traverse of Group XXI, (original claims 64 – 78 and newly added claims 88 – 92, as they read on sequences of SEQ ID NOS: 7 and 8) in the reply filed on 01/20/2006 is acknowledged.

3. Applicant's addition of new claims readable on SEQ ID NO:6, which has not been presented in the original claims, necessitated an additional Species election requirement, which is set forth herein:

This application contains claims directed to the following patentably distinct Species of the claimed Invention, wherein the human BTLA protein comprises:

A. SEQ ID NO:8, or
B. SEQ ID NO:6.

These species are distinct because their structures, physicochemical properties and mode of action are different, and they do not share a common structure that is

disclosed to be essential for common utility. Furthermore, the examination of these species would require different searches in the scientific literature. As such, it would be burdensome to search these Species together.

However, in the interest of compact prosecution, examination has been extended to include the sequences of both species of human BTLA protein.

4. Claims 1 – 63 and 79 – 87 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 64, 67, 68, 70, 71, 73 – 78, and 88 – 92 are under consideration in the instant application.

5. Applicant's request to correct inventorship under 37 CFR 1.48(b), filed 01/27/2006, is acknowledged, and has been granted. James P. Allison and Xingxing Zhang have been deleted as co-inventors of the instant application. The co-inventors of the instant application are Kenneth P. Murphy, Norihiko Watanabe, Theresa L. Murphy, and Jianfei Yang.

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least in Figure 4 *are not accompanied by SEQ ID Numbers.* Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9

nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification and the claims accordingly. The SEQ ID Numbers for a sequence shown in a drawing may be incorporated either as part of the drawing or in the Brief Description of the drawing.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

7. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

However, the provisional application USSN 60/390,653 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the subject matter claimed in the instant application. Specifically, insufficient support was identified for BTLA sequences of SEQ ID NO: 6, 7, or 8.

Likewise, the provisional application USSN 60/438,593 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the subject matter claimed in the instant application. It is acknowledged that the provisional application discloses in Figure 19 the amino acid sequence of a human BTLA allelic variant of SEQ ID NO:6. However, this is not seen as sufficient support under 35 U.S.C. 112 for the claimed limitations of nucleic acid of SEQ ID NO:7 or nucleic acids encoding polypeptides of SEQ ID NO:6 or 8.

It is noted that with regard to claims 64, 67, 68, 70, 73 – 78, and 88 – 91, amended or added in an amendment filed 01/20/2006 (i.e. subsequent to the filing date of the instant application), no determination of priority date is being made at this time, in

view of the New Matter rejection set forth below. For examination purposes, these claims are presently treated as if their priority date is the filing date of the instant application, i.e. 06/20/2003.

Claims 71 and 92 have been accorded the priority of the filing date of the instant application, i.e. 06/20/2003.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

8. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

9. Applicant's IDS, filed 08/02/2004, is acknowledged, and has been considered.

10. The use of trademarks has been noted in this application (e.g. RNeasy on page 72). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

11. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

Applicant is requested to identify the written support for claims 64, 67, 68, 70, and 71, particularly the following claimed limitations:

"a recombinant BTLA nucleic acid, comprising a nucleotide sequence having at least about 85% identity to the nucleotide sequence set forth in SEQ ID NO:7;"

"comprising an allelic variant of the nucleotide sequence set forth in SEQ ID NO:7;"

"having BTLA signaling activity;" and

"comprising the nucleotide sequence set forth in SEQ ID NO:7."

Alternatively, Applicant is invited to amend the specification to provide antecedent basis for the claimed subject matter.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 70 is rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 70 is indefinite in the recitation of "BTLA signaling activity," because the metes and bounds of the phrase are unclear. The specification discloses at page 4, lines 4 – 9, examples of various aspects of "BTLA signaling activity," wherein "BTLA signaling can inhibit TCR-induced T cell responses, such as cell cycle progression, differentiation, survival," etc; however, in the absence of a limiting definition of "BTLA signaling activity," one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 64, 67, 68, 70, 73 – 78, and 88 – 91 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a New Matter rejection.*

Applicant's amendment asserts that no New Matter has been added and points to the specification at pages 18 and 25, and to original claims 64, 68, and 73 for support for the newly added claim limitations. However, the specification does not appear to provide an adequate written description of these limitations.

Specifically, regarding the amendment to claim 64, the original claim 64 recites at least about 70% identity to SEQ ID NO:7, while the specification at page 25 discloses various percentages of identity to nucleic acids encoding B7x, but not BTLA proteins.

Regarding the amendment to claim 73, the specification at page 25, lines 27 – 31, discloses a BTLA polypeptide having at least 85% identity to the amino acid sequence set forth in Figure 19. However, the human BTLA polypeptide shown in

Figure 19 has the sequence of SEQ ID NO:6, not SEQ ID NO:8, as instantly claimed. Furthermore, although the original claim 73 recites a BTLA protein comprising the amino acid sequence set forth in SEQ ID NO:8, it is not seen as providing sufficient support under 35 USC 112, first paragraph, for the recitation of "having at least about 85% identity" to SEQ ID NO:8.

Claims 67, 68, 70, 74 – 78, and 88 – 91, dependent on either claim 64 or claim 73, encompass in their scope the newly added limitations lacing support in the specification or claims as originally filed, and therefore are subject to this New Matter rejection.

Claims 71 and 92 are limited to subject matter presented in the specification or claims as originally filed, and therefore are not included in this rejection. (It is noted that the transitional phrase "having" in the original claim 71 is interpreted as open language, i.e. as equivalent in scope to "comprising.")

The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the New Matter in the response to this Office Action. Alternatively, Applicant is invited to clearly point out the written support for the instant limitations.

16. Claims 64, 67, 68, 70, 73 – 78, and 88 – 91 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *Written Description* rejection is set forth herein.

Applicant is not in possession of the following claimed embodiments:

A. a nucleic acid comprising a nucleotide sequence set forth in SEQ ID NO:7, or encoding a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:6 or 8;

B. a nucleic acid having at least about 85% (or 90% or 95%) identity to SEQ ID NO:7, or encoding a polypeptide having at least about 85% (or 90% or 95%) identity to SEQ ID NO:8;

C. a nucleic acid comprising a splice variant or an allelic variant of SEQ ID NO:7.

The instant claims do not provide sufficient structural and functional characteristics of the genus of nucleic acids encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure. Consequently, the specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such

identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Regarding the instant claim limitations, the specification does not appear to provide an adequate written description for the following reasons:

"Percent identity," "allelic variants," and "splice variants."

The claims recite a genus of nucleic acids having at least about 85% (or 90% or 95%) identity to SEQ ID NO:7, or encoding a polypeptide having at least about 85% (or 90% or 95%) identity to SEQ ID NO:8. Applicant has disclosed only a single nucleic acid sequence encoding human BTLA protein (SEQ ID NO:7), and two amino acid sequences of allelic variants of human BTLA (SEQ ID NOS:6 and 8), and thus has disclosed only two "variants". In the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1): 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

The term "allelic variants" encompasses one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms. Similarly, a "splice variant" is a reference to a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of the polypeptide. Applicant has not provided sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, that provides a sufficient written description of the allelic variants or splice variants of human BTLA protein of SEQ ID NO:8, other than a single allelic variant of SEQ ID NO:6. The disclosure of a mouse BTLA splice variant and several allelic variants is not seen as sufficient written description of human BTLA variants.

Thus the recitation of percent identity language, especially in the absence of *a testable function*, does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Fragments.

The instant claim language contains recitations of "a nucleic acid comprising **a** nucleotide sequence set forth in SEQ ID NO:7," and thus encompasses in its breadth any fragments, of any length or structure, of SEQ ID NO:7.

However, the specification does not appear to have provided sufficient written description as to which fragments SEQ ID NO:7 would encode functional protein fragments. Neither does the specification appear to have provided any structural motifs or working examples of functional fragments of BTLA. Further, the term "comprising" is open-ended and extends the polypeptide to include additional non-disclosed sequences on either or both sides (i.e. it reads on nucleic acids encoding fusion proteins comprising fragments of BTLA). As the term "comprising" is applied to sequences other than full length polypeptides, there does not appear to be sufficient written description in the specification as filed to convey to the skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention.

A skilled artisan at the time the invention was made was aware that most fragments of proteins, when incorporated into fusion proteins, would result in non-functional products. For example, Peach et al. (J. Exp. Med., 1994, 180: 2049 – 2058; see entire document) describe a number of CD28/CTLA4 chimeric proteins fused to an immunoglobulin constant region, such that the constructs differ from each other by the regions of CD28 and/or CTLA4 present in the fusion protein (see entire document, in particular, e.g. Figure 3). Only a few of these fusion proteins are functional, depending on which specific region of CD28 and/or CTLA4 is present in the fusion protein (e.g. Table 1 at page 2053). Thus the generic recitation of the language which encompasses "fragments," in the absence of written description of the specific nature of functional BTLA fragments, does not convey to the skilled artisan that the inventors, at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

17. Claims 64, 67, 68, 70, 73 – 78, and 88 – 91 are rejected under 35 **U.S.C. 112, first paragraph**, because the specification, while being enabling for a recombinant BTLA nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO:7, or encoding a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:6 or 8, does not reasonably provide enablement for the following claimed embodiments:

A. a nucleic acid comprising a nucleotide sequence set forth in SEQ ID NO:7, or encoding a polypeptide comprising an amino acid sequence set forth in SEQ ID NO:6 or 8;

B. a nucleic acid having at least about 85% (or 90% or 95%) identity to SEQ ID NO:7, or encoding a polypeptide having at least about 85% (or 90% or 95%) identity to SEQ ID NO:8;

C. a nucleic acid comprising a splice variant or an allelic variant of SEQ ID NO:7.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that the recitation of "a nucleic acid comprising **a** nucleotide sequence set forth in SEQ ID NO:7" encompasses in it s scope nucleic acids that comprise the full-length sequence of SEQ ID NO:7 as well as any portion of SEQ ID NO:7.

The specification discloses a single nucleic acid sequence encoding human BTLA protein (SEQ ID NO:7), and two amino acid sequences of allelic variants of human BTLA (SEQ ID NOS:6 and 8). The instant specification also discloses a mouse splice variant of BTLA and several mouse allelic variants of BTLA sequence. The instant claims encompass in their breadth any nucleic acid at least about 85% identical to the disclosed sequence, as well as any fragments, allelic variants, or splice variants. However, there is insufficient enabling description of the claimed genus of nucleic acids in the absence of defining the relevant identifying characteristics such as the structure or other physical and/or chemical characteristics of the claimed genus. The instant claims do not provide adequate structural and functional characteristics of the genus of nucleic acids encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure. Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"Percent identity," "allelic variants," and "splice variants."

The claims recite a genus of nucleic acids having at least about 85% (or 90% or 95%) identity to SEQ ID NO:7, or encoding a polypeptide having at least about 85% (or 90% or 95%) identity to SEQ ID NO:8. Applicant has disclosed only a single nucleic acid sequence encoding human BTLA protein (SEQ ID NO:7), and two amino acid

sequences of allelic variants of human BTLA (SEQ ID NOS:6 and 8), and thus has disclosed only two "variants". In the absence of a particular testable function and some structural basis for that function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1): 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

The term "allelic variants" encompasses one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms. Similarly, a "splice variant" is a reference to a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of the polypeptide. Applicant has not provided sufficient biochemical information (e.g. nucleic acid sequences, etc.) that distinctly identifies the allelic variants or splice variants of human BTLA protein of SEQ ID NO:8, other than a single allelic variant of SEQ ID NO:6. The disclosure of a mouse BTLA splice variant and several allelic variants is not seen as sufficient enabling description of human BTLA variants.

In view of this unpredictability, the skilled artisan would not reasonably expect a generically recited polypeptide having at least about 85% identity SEQ ID NO:8, or encoded by a nucleic acid having at least about 85% identity to SEQ ID NO:7, to share the same function as the polypeptide of SEQ ID NO:8, and there is insufficient guidance to direct the skilled artisan as to such functional sequences. Thus the recitation of percent identity language does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

Fragments.

The instant claim language contains recitations of "a nucleic acid comprising **a** nucleotide sequence set forth in SEQ ID NO:7," and thus encompasses in its breadth any fragments, of any length or structure, of SEQ ID NO:7.

However, the specification does not appear to have provided sufficient guidance as to which fragments SEQ ID NO:7 would encode functional protein fragments. Neither does the specification appear to have provided any structural motifs or working examples of functional fragments of BTLA. Further, the term "comprising" is open-ended and extends the polypeptide to include additional non-disclosed sequences on either or both sides (i.e. it reads on nucleic acids encoding fusion proteins comprising fragments of BTLA). As the term "comprising" is applied to sequences other than full length polypeptides, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various fusion proteins encompassed by the instant claims.

A skilled artisan at the time the invention was made was aware that most fragments of proteins, when incorporated into fusion proteins, would result in non-functional products. For example, Peach et al. (J. Exp. Med., 1994, 180: 2049 – 2058; see entire document) describe a number of CD28/CTLA4 chimeric proteins fused to an immunoglobulin constant region, such that the constructs differ from each other by the

regions of CD28 and/or CTLA4 present in the fusion protein (see entire document, in particular, e.g. Figure 3). Only a small subset of these fusion proteins are functional, depending on which specific region of CD28 and/or CTLA4 is present in the fusion protein (e.g. Table 1 at page 2053). Thus it would require undue experimentation of the skilled artisan to determine which parts of which proteins would be useful when incorporated into the instantly claimed fusion proteins.

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 64, 67, 68, 70, 71, 73, and 88 – 92 are rejected under **35 U.S.C. 102(a)** as being anticipated by Watanabe et al. (NCBI Accession Number AY293286; 05/08/2003; see entire document).

Watanabe et al. teach a nucleic acid identical in sequence to the instantly claimed SEQ ID NO:7, which encodes the instantly claimed polypeptide of SEQ ID NO:8 (see entire document), as shown by the attached alignment. It is noted that the instantly claimed SEQ ID NO:7 is itself one of possible splice variants of SEQ ID NO:7, and encodes one of possible allelic variants of human BTLA. Since the polypeptide encoded by the nucleic acid sequence taught by Watanabe et al. is the same as instantly claimed, it inherently possesses the same structural and functional properties, including a transmembrane region and BTLA signaling activity.

Therefore, the reference teachings anticipate the instant claimed invention.

20. Claims 64, 67, 68, 70, 71, 73 – 76, and 88 – 92 are rejected under **35 U.S.C. 102(a)** as being anticipated by Watanabe et al. (NCBI Accession Number AY293286; 05/08/2003; see entire document) as evidenced by Watanabe et al. (Nature Immunol., 2003, 4: 670 – 679; see entire document) and pGEM-T Technical Manual (Promega, 2005, page 2).

Watanabe et al. (NCBI Acc. No. AY293286) have been discussed supra, and teach a nucleic acid identical in sequence to the instantly claimed SEQ ID NO:7, which encodes the instantly claimed polypeptide of SEQ ID NO:8. Watanabe et al. (Nature Immunol.) provide evidence that prior to obtaining the sequence disclosed as NCBI Acc. No. AY293286, the authors amplified human BTLA cDNA and inserted it into the GEM-T Easy vector. pGEM-T Technical Manual provides evidence that the GEM-T vector contains T7 and SP6 promoters (page 2 second paragraph), i.e. is an expression

vector. A skilled artisan at the time the invention was made was apprised that the procedure of cloning a PCR product into a plasmid vector includes propagating the construct through E. coli host cells. Therefore, inherent in the teachings of Watanabe et al. (NCBI Acc. No. AY293286) is an expression vector comprising a recombinant BTLA nucleic acid, and a host cell comprising such vector.

Therefore, the reference teachings anticipate the instant claimed invention.

21. Claim 64, 67, 68, 70, 73 – 78, and 88 – 92 are/is rejected under **35 U.S.C. 102(e)** as being anticipated by Clark et al. (US Pat. Pub. No. 2004/0091884; see entire document).

Clark et al. teach and claim an isolated recombinant nucleic acid (SEQ ID NO:1, see e.g. Figure 1, and claims 1 – 3) which is 98.2% identical to the instantly claimed SEQ ID NO:7, and encodes a polypeptide which is 100% identical and 97.4% identical to the instantly claimed SEQ ID NO:6 and 8, respectively, as shown by the attached alignments. Clark et al. further teach and claim expression vectors comprising said nucleic acid, host cells comprising said vectors, and methods of producing the polypeptide encoded by said nucleic acids using host cells comprising the vectors (see entire document, in particular, e.g. claims 4 – 8 and paragraphs 0043, 0051, and 0052).

It is noted that the instantly claimed SEQ ID NO:7 is itself one of possible splice variants of SEQ ID NO:7, and encodes one of possible allelic variants of human BTLA. Since the polypeptide encoded by the nucleic acid sequence taught by Clark et al. is the same as instantly claimed, it inherently possesses the same structural and functional properties, including a transmembrane region and BTLA signaling activity.

Therefore, the reference teachings anticipate the instant claimed invention.

22. Conclusion: no claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI, Ph.D.
Patent Examiner
Art Unit 1644

March 14, 2006

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TC 1600
3/15/06

Attachment: 5 pages.